

### **III. REMARKS**

#### ***Claim Status***

Claims 17-18 and 22-28, 30-32 and 34 are active in the case.

#### ***Claim Rejections - 35 USC § 103***

Claims 17-18, 22-28, 30-32 and 34 are rejected under 35 U.S.C. 103(a) as being unpatentable over Dasseux et al., (WO 99/16458 published April 8, 1999) in view of Rozek et al., (Biochemistry. 1995. Vol. 34, pages 7401-7408).

Claims 17-18, 22-28, 30-32 and 34 are rejected under 35 U.S.C. 103(a) as being unpatentable over Dasseux et al., (US Patent 6,004,925 published December 21, 1999) in view of Rozek et al., ( Biochemistry. 1995. Vol. 34, pages 7401-7408).

The examiner states that applicants previous arguments about the differing structural similarities and differences as argued by applicants is irrelevant, since the rejection is based on ApoA-I agonist, and peptides which act as ApoA-I agonist, not about the differences between ApoA-I and ApoC-I.

Thus, the issue under consideration is still the same as previously, and the examiner has commented in applicant's last response. The examiner found applicant's last response not persuasive, and/or addressing not the proper items for rejection.

According to the Examiner, the gist of the 103 rejection is that the prior art teaches that ApoC-I meets the

qualifications of being an ApoA-1 agonist and hence would be effective in treating septic shock.

The literature references in brackets below are:

1. Berbee et al. FASEB Journal 2006; 20: 1560-1569
2. Rensen et al J Clin Invest 1997 ; 99 : 2438
3. Lynch et al. J Biol Chem 2003; 278: 48529
4. Berbee et **al.** J Lipid Res 2005 ; 46 : 297
5. Gautier et al- J Biol Chem 2000 ; 275 : 37504
6. De Haan W et al. Biochem Biophys Res Commun 2008; 377: 1294
7. Jong et al. Biochem J **1999**; 338; 281

The main argument of the Examiner of ApoC-1 being an Apo-I agonist is that both ApoA1 and ApoC1 have a 22 amino acid consensus sequence. This is not unexpected since all apolipoproteins (Apo) have such sequences. These sequences are involved in binding lipids, actually the most important property of apolipoproteins. Although all apolipoproteins bind lipids via their helical structures, only a small number of them (e.g. ApoC1, ApoE and ApoA1) also bind LPS. The structures involved in LPS binding in ApoC1 (1), ApoE (2) and ApoA1 are not necessarily equal to their lipid binding helical structures and moreover, the LPS binding structures present in ApoC1 (sequence KVKEKLLK), ApoA1 (unknown) and ApoE (sequence

LRVRLASHLRKLRKRL) are clearly different.

The LPS-binding domain of ApoC1 is largely located in the C-terminal helix (1), whereas the LPS-binding domain of ApoE is reported to overlap the receptor-binding domain of ApoE, residing in -only- the fourth N-terminal helix of apoE (3). Furthermore, even very similar apolipoproteins can be very

different in LPS binding. ApoC3 that is very similar to ApoE1 in helical structure does not bind LPS, but, being an apolipoprotein does bind lipid via its helical sequence. Even when apolipoproteins do bind LPS such as e.g. ApoC1 and ApoE, the effect in vivo can be very different. ApoC1 retards uptake of LPS from the bloodstream, whereas ApoE accelerates LPS uptake. So, certainly not all peptides based on apolipoproteins do bind LPS and lipid binding and LPS binding are mediated by different structural elements, of which the LPS binding elements are only present in some apolipoproteins and when present can be structurally very different between apolipoproteins.

Apolipoproteins have generally multiple functions that can differ between the various apolipoproteins, although they all share the property of binding lipids. Both ApoA1 and ApoC 1 activate LCAT enzymatic activity, but ApoC 1 inhibits LPL (4) and CETP (5) enzymatic activity, whereas ApoA1 has no effect on LPL (4) and CETP (5). ApoA1 inhibits binding of HDL to the HDL receptor SR-B 1 (6) and inhibits binding of VLDL to the VLDL receptor (7), whereas ApoA1 actually causes binding of HDL to SR-B1, and has not been reported to inhibit the VLDL receptor.

Based on all these observations one cannot make general conclusions on similarity in functional activities based on similarity in structural elements within the group of apolipoproteins\_ Within ApoC1 the structure KVICEKLK is very important in binding of LPS since the mutated version of this sequence (K replaced by A) AVAEALA has severely impaired LPS binding. Although this sequence is very important in LPS

binding it is not sufficient per se, it has to be part of somewhat longer sequences in order to reach full functionality.

In summary it is not possible to predict the LPS binding and the effect on sepsis of ApoC1 from structural and functional properties of ApoA1.

Another interesting observation is that the effects of ApoA1, ApoE and ApoC 1 in vivo in sepsis are very different. ApoA1 and ApoE decrease the effective concentration of LPS and as such decreases the inflammatory response to LPS, whereas ApoC1 actually might increase the LPS concentration thereby enhancing the LPS-induced inflammatory response and activating the immune system to attack the bacteria.

The above arguments thus show that the assumption of the Examiner that any ApoA-1 agonist, where the agonist activity would be structurally related, would have the desired therapeutic effects, fails because of the inherent variability of structurally related activity of the apolipoproteins.

Favorable reconsideration is respectfully requested.

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The Commissioner is hereby authorized to charge payment for any fees associated with this communication or credit any over payment to Deposit Account No. 14-1263.

Respectfully submitted,

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A handwritten signature in black ink, appearing to be "Serle Ian Mosoff", written over a horizontal line.

By \_\_\_\_\_

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